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10/538,514	06/09/2005	Tsuyoshi Naganuma	Q88061	1878

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
05/12/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

sughrue@sughrue.com
PPROCESSING@SUGHRUE.COM
USPTO@SUGHRUE.COM

Office Action Summary	Application No.	Applicant(s)	
	10/538,514	NAGANUMA ET AL.	
	Examiner	Art Unit	
	WALTER WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,11,12 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 8, 9, 11, 12 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 2/23/2011, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112—New by Amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1, 8, 9, 11, 12, 27-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has amended the instant claim 1 the recite the phrase “as an extracellular ingredient”. The phrase constitutes new matter since there is no support in the disclosure for this phrase.

Applicant indicated that support for this phrase can be found in the description of Examples 1 and 2 in the specification. The relevant section of the specification reads, "A mixture of 1.8 parts of magnesium stearate and 1.8 parts of sodium lauryl sulfate was

added to the sieved granules and mixed for 5 minutes, and the mixture was filled into a capsule shell to prepare a capsule . . . " (see pg. 35 lines 1-3; see also pg. 35, lines 15-18). It is noted that section of the specification does not account for calcium stearate or talc. Thus there is no support for calcium stearate or talc as "extragranular ingredient". Furthermore, it is apparent that sodium lauryl sulfate and magnesium stearate are added to sieved granules, however, the composition is subsequently mixed for 5 minutes. It is not clear whether the mixing creates another granule or granules, which would cause magnesium stearate and sodium lauryl sulfate to be intra-granular ingredients. It should also be noted here, that the disclosure provides does not define "granule".

112 2nd, Indefinitenes

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, 9, 11, 12, 27-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "extragranular ingredient" in claim 1 is a relative term which renders the claim indefinite. The term "extragranular ingredient" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear to what extent an ingredient may be "extragranular" and still

satisfy the requirement of the claim. For example, the disclosure, which is discussed above, indicates that magnesium stearate and sodium lauryl sulfate are mixed with sieved granules. Applicant attempts to argue implicit support from working examples. While these provide illustrations of what might be “extragranular”, they do not define the general term. However, assuming that applicant’s working example components remain attached to the outside of the granules, an unmixed, separate component composition comprising magnesium stearate and sodium lauryl sulfate might (?) also be “extragranular”. It is not clear what is meant by this phrase such that the artisan would reasonably appreciate the metes and bound of what is encompassed by this phrase.

For the purpose of examination, the term "extragranular" will be broadly interpreted as a component outside of the granule, e.g. a lubricant, coating, capsule or part of a separate component composition.

Claim Rejections - 35 USC § 103--Previous

Claims 1, 8, 9, 11, 12 and 27-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kitazawa et al., (US 5,387,603) in view of Ishihara et al., (US 2002/0177593) and in further view of Salpekar et al., (US 4,757,090) and Shah (US 5,370,878) and Tasaka et al., (US 2002/0173526).

Since the prior art teaches the use of magnesium stearate and sodium lauryl sulfate as lubricants, the artisan would have reasonably expected them to be "extragranular" (see Ishihara et al. at paragraphs [0618], [0626], [0620], and [0596]).

Response to Arguments

a) Declaration

The supplemental declaration filed 2/23/2011 is acknowledged. Affiant presented a new showing of capsules of the present invention, Examples 1, 2 and C, and comparative capsules, N, O, B, H and Q. Applicant indicated that capsule Q contains sodium lauryl sulfate as an intragranular ingredient and was prepared as described at col. 4, lines 29-32 of Shah. Affiant's data shows results of storage stability, i.e. 60℃ for 7 days, and dissolution rates. Affiant states that the results (Table 1) show that dissolution rates of capsules N, O and B were notably lower than those of Examples 1 and 2 of the present invention, and that "not only partially pregelatinized starch but also D-mannitol and sodium lauryl sulfate are necessary for imparting immediate dissolution property" (see Declaration at pg. 3, 3rd paragraph).

Affiant also indicated that capsule Q, comprising sodium lauryl sulfate as an intragranular ingredient, showed a considerably lower dissolution rate and remarkable decomposition, compared to Examples 1 and 2. Affiant concluded that "sodium lauryl sulfate is necessary as an extragranular ingredient for imparting immediate dissolution property and good storage stability" (see Declaration at pg. 4, 1st paragraph). Applicant also concluded that "the combination of lubricant and sodium lauryl sulfate as an extragranular ingredient provides the capsule of the present invention with much higher dissolution properties as compared to capsules containing lubricant alone".

Affiant's showing is not persuasive of non-obviousness.

To begin, it should be noted here that the Affiant presented a data set, filed 4/8/2010, which indicated that the combination of two different starches, PCS and Starch 1500, were directly responsible for the dissolution rate of the composition. The examiner agreed with this showing (see Non-Final Rejection filed 08/30/2010, at pg. 6). Although Examples 1 and 2 continue to comprise both PCS and Starch 1500, affiant contends that it is not the mixture of PCS and Starch 1500 that provides the dissolution rate, but the addition of sodium lauryl sulfate. It should also be noted here that this conclusion is in conflict with the previous showing filed 4/8/2010, which showed Capsule A, of Table 1, in absence of sodium lauryl sulfate and magnesium sulfate having a dissolution rate of 85% after 15 minutes (this satisfies the limitation of the claim in regard to dissolution rate) (see pg. 11 of Declaration filed 4/8/2010). Thus it appears that sodium lauryl sulfate is **not** necessary for imparting immediate dissolution as postulated by affiant. Furthermore, applicant's results are not commensurate in scope with the invention as claimed since the results were seen with Starch 1500 and/or PCS, while the instant claims broadly recite "partially pregatinized starch". The results appear to depend on one or both of these specific starches and the use of these specific types of starches do not provide an adequate basis for concluding that pregelatinized starches, in general, would behave in the same way.

Secondly, it is not clear why sodium lauryl sulfate is added as an intragranular ingredient, and is indicated as being supported by Shah, when Shah does not teach using sodium lauryl sulfate or "intragranular" ingredients, per se (see Shah at col. 4, lines 29-32).

Furthermore, applicant's showing in regard to enhanced dissolution with sodium lauryl sulfate does not appear to be unexpected. It is noted that each capsule has been coated with magnesium stearate, which is a waxy substance. Since each composition was dissolved in water (see Specification at pg. 33, line 1), one would not expect a waxy coated capsule to rapidly dissolve. Logically, one would expect a detergent, i.e. sodium lauryl sulfate, to improve dissolution, since detergents emulsify fats. For the purpose of rebutting affiant's conclusions of unexpected results, the examiner cites Ong et al.(International Journal of Pharmaceutics, 1993), which studied the role of various surfactants on drug-excipient interactions resulting from prolonged powder mixing with magnesium stearate (see Abstract). The results of Ong et al. "indicate that some surfactants in a concentration as little as 0.1% (1:5 ww ratio to magnesium stearate) can alleviate the deleterious effect of magnesium stearate on prolonged mixing of powder, i.e. the decrease in the dissolution rate of the drug (see *Id.*). Ong et al. further states that the interaction of surfactant with magnesium stearate reduces the net coverage of the drug-excipient by magnesium stearate, and that water-soluble hydrophilic surfactants would help to detach any magnesium film covering the drug-excipients, thus alleviating the decrease in drug dissolution caused by magnesium stearate (see *Id.*). The reference specifically teaches that magnesium stearate reacts strongly with sodium lauryl sulfate, freeing the magnesium stearate film from the drug-excipient agglomerates (see pg. 232, right column, 2nd paragraph). Thus, affiant's results showing improved dissolution with the addition of sodium lauryl sulfate do not appear to be unexpected.

b) Remarks

1) Applicant argues against each reference individually concluding each time that the reference "fails to teach or suggest the capsule of the present invention and the advantageous effects of the present capsule."

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The reference to Kitazawa et al. teaches the claimed indoline compound and provides motivation for formulating a tablets and capsules, as well as teaching an acceptable dosage range for oral administration. Ishihara et al. teaches the same indoline compound and provides motivation for using pregelatinized starch, light-shielding coating agents, D-mannitol, magnesium stearate and sodium lauryl sulfate when formulating tablets and capsules. Shah and Tasaka et al. provide motivation for using Starch 1500 and PCS, as pregelatinized starches, and Salpekar et al. teaches that it is the pregelatinized starches that that give a short dissolution time, e.g. about 20 minutes or less for 80% or more of the active compound. The test of obviousness is not the express suggestion of the claimed invention in any or all of the references, but what the references taken collectively would suggest to those of ordinary skill in the art. The artisan would have understood that the various features of the references could be combined to obtain the expected additive results, i.e. formulating a capsule comprising the claimed indoline compound, D-mannitol, partially pregelatinized starch, magnesium

stearate, sodium lauryl sulfate, where the composition has an 85% dissolution rate in not more than 15 minutes in a dissolution test.

2) Applicant argues that the teaching of Shah on partially pregelatinized starch would not lead a person ordinarily skilled in the art to expect the advantageous effects of immediate dissolution and excellent storage stability exhibited by the present invention (see pg. 11, 2nd paragraph).

This argument is not persuasive.

In regard the pregelatinized starch, the prior art (Salpekar et al.) teaches that the use of pregelatinized starch directly attributes to a short dissolution time, e.g. about 20 minutes or less for 80% or more of the active compound (see abstract, and col. 2, lines 60-66). Thus, an 85% dissolution time not more than 15 minutes, would be reasonably expected.

In regard to storage stability, it is noted that this is not a feature of the claimed invention, and it is not clear how applicant's data supports an unexpected result over the prior art. Applicant presented data showing 0.71%, 0.46%, and 2.31% decomposition for capsules of the present invention, but failed to show stability results for Comparative examples N, O, B, and H. There was no explanation for the absence of this data, nor was there an explanation for why stability results were shown only for Comparative example Q. Applicant indicated that Comparative example Q represents the prior art formulation of "Shar", which examiner assumes is "Shah (US 5,370,878)". However, Shah does not teach sodium lauryl sulfate, so it is not clear how Comparative

capsule Q represents Shah. Furthermore, applicant's data seems to suggest that starch PCS contributes to storage stability since decomposition increased when it was removed (compare Example 2 and Capsule C of Table 1). However, the instant claims are not commensurate in scope with these results, since starch PCS is no longer required. It is also noted that the dissolution rate % also decreased when starch PCS was removed.

3) Appliance argues that the dissolution rate of capsules not containing D-mannitol in the particulate, are notably lower than those of the capsule on the present invention (see pg. 11,5th paragraph).

This argument is not persuasive.

D-mannitol does not appear to contribute to increased dissolution, since Comparative capsule O, without D-Mannitol, had a higher dissolution %, i.e. 32%, than Comparative capsule B, with D-Mannitol, i.e. 8%.

4) Applicant argues that there is no motivation that would lead a person ordinarily skilled in the art to combine the granulated compositions containing highly water soluble acetaminophen for direct compression tables as taught by Shar or Salpekar with D-mannitol taught by Ishihara for developing capsules containing hardly water soluble KMD-3213 in place of acetaminophen and having immediate dissolution property and good storage stability (see pg. 12, last paragraph).

This argument is not persuasive.

The primary reference, Kitazawa et al., provides motivation for formulating a capsule of the claimed indoline compound. Other references were combined with this teaching in regard to excipients that the artisan would have reasonably been expected to use in regard to formulating a capsule of the indoline compound of Kitazawa et al. There is no need to replace acetaminophen with KMD-1332, since the prior art credits the excipients with providing a short dissolution time. Salpekar taught that the use of pregelatinized starches produces a short dissolution time, e.g. about 20 minutes or less for 80% or more of the active compound, and Shah teaches using pregelatinized Starch 1500, for producing a short dissolution time.

5) Applicant argues that the addition of sodium lauryl sulfate as an extragranular ingredient provides the capsule of the present invention with extremely higher storage stability as compared to capsules containing sodium lauryl sulfate as an intragranular ingredient (see pg. 13, 2nd paragraph). .

This argument is not persuasive.

The prior art does not teach using sodium lauryl sulfate as an intragranular ingredient. Thus, it is not clear why applicant is making this distinction. Ishihara et al. describes sodium lauryl sulfate as a lubricant. Therefore, the artisan would reasonably expect it to be used for coating the outside of the tablet or capsule. Based on applicant's showing at Table 1, it appears that starch PCS contributes to storage stability, as opposed to sodium lauryl sulfate. Example 1, 2, and Capsule C, each contained the same amount of sodium lauryl sulfate, but Capsule C, had a dramatic

increase in decomposition, i.e. 2.31% compared to Example 1 (0.78%), and Example (0.46%). The major difference between these examples was the absence of starch PCS from Capsule C. Thus, it does not appear to follow that sodium lauryl sulfate contributes to storage stability. It is also noted the Capsule Q, the only other example to have a storage stability results (7.44%), also lacked starch PCS.

The examiner relies on the rebuttal to Affiants conclusions made above in response to applicants conclusions in the Remarks, with regard to dissolution properties of sodium lauryl sulfate (Remarks at pg. 13, 2nd paragraph), alleged unexpected results (Remarks at pg. 14) and applicant's showing (Remarks at pg. 10).

Technological Background

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ong et al., "Drug-excipient interactions resulting from powder mixing. VI. Role of various surfactants". International Journal of Pharmaceutics, 96 (1993) 231-242. Ong et al. is pertinent for teaching that sodium lauryl sulfate increases dissolution of a drug-excipient coated with magnesium stearate.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612